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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1656	4

DATE MAILED: 12/12/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/920,571	LASKEN ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1656	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 20-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 20-64* is/are rejected.

7)☒ Claim(s) *59 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Objections

1. Claims 59 and 60 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

2. Applicant is advised that should claim 1 be found allowable, claim 62 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 50, 56, 59 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 50 recites the limitation "said 3'-terminal nucleotide" in page 48, line 14. There is insufficient antecedent basis for this limitation in the claim.

B) Regarding claims 56, 59 and 60 (dependent on claim 56), the phrase "such as" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 1, 2, 5-7, 10, 11, 20, 22-24, 26-29, 31, 33, 35-40, 42, 44-45, 48, 49, 51-54 and 62-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Lizardi (U.S. Patent No. 5,854,033), referred to as Lizardi-1.

A) Lizardi-1 teaches amplification of circular DNA molecule by a rolling circle method . The rolling circle amplification (RCA) involves hybridization of a primer to amplification target circle (ATC) followed by amplification using strand-displacing DNA polymerase (column 19, lines 20-31), resulting in a DNA molecule with multiple repeats of the ATC, usually referred to as tandem sequences DNA (TS-DNA).

In one embodiment of the amplification, strand displacement cascade amplification, (SDCA), secondary and tertiary primers are used, with sequences complementary to the ATC (col. 25, lines 36-49). The SDCA can be performed simultaneously with RCA, resulting in exponential amplification (col. 28, lines 8-18; col. 26, lines 61-66).

B) The primers are from 10 to 35 nucleotides long (col. 10, line 14).

C) The primers can contain a region at the 5'-end which is non-complementary to the ATC (col. 10, lines 16-22).

D) The ATC is a circular, single-stranded DNA molecule, of 40 to 1,000 nucleotides (col. 9, lines 25-29.

E) The ATC can be derived from a single-stranded bacteriophage (col. 35, lines 50-59).

F) Radioactive nucleotides can be used in the amplification (col. 21, lines 22-25).

G) Primers may include modified nucleotides to make them exonuclease-resistant. The phophorothioate nucleotides can be positioned at the 5'-end of the primer (col. 10, lines 24-28; col. 13, lines 27-31).

H) Fluorescence-labeled nucleotides can be used (col. 11, lines 2-5).

I) The DNA polymerases to be used include: bacteriophage ϕ 29 DNA polymerase, phage M2 DNA polymerase, VENT DNA polymerase, Klenow fragment of DNA polymerase I, T5 DNA polymerase, PRD1 DNA polymerase, T4 DNA polymerase holoenzyme (col. 17, lines 66-67, col. 18, lines 1-11).

J) Lizardi-1 teaches oligonucleotides attached to solid support, including glass (col. 14, lines 34-43, 65-67; col. 15, lines 1-10).

7. Claims 1, 2, 5-7, 10, 11, 20, 22, 23, 26, 36, 37, 38, 51, 52, 62-64 are rejected under 35 U.S.C. 102(e) as being anticipated by Kingsmore et al. (U.S. 2001/0041340 A1).

A) Kingsmore et al. teach a method of nucleic acid amplification comprising:

a) mixing at least one single-stranded non-circular first-stage oligonucleotide primer (P1) and at least one single stranded first-stage amplification target circle (ATC1) to produce a primer-ATC sample mixture;

b) incubating said primer-ATC1 sample mixture under conditions that promote hybridization between the oligonucleotide primer and the amplification target circle

to form a hybridized primer-ATC1 sample mixture and allowing sufficient time to pass for hybridized primer-ATC1 complexes to form;

c) mixing a DNA polymerase and at least two deoxynucleotide triphosphates with said hybridized primer-ATC1 sample mixture to produce a polymerase-primer-ATC1 sample mixture and incubating the polymerase-primer-ATC1 mixture under conditions that promote replication of the amplification target circles to form a primary tandem sequence DNA (TS-DNA);

d) adding to said polymerase-primer-ATC1 mixture at least one second-stage primer oligonucleotide (P2) comprising a first portion, or segment, having a sequence complementary to one or more sequences present in said primary TS-DNA and a second portion, including a free 3'-OH end, having a sequence not complementary to said primary TS-DNA, under conditions promoting hybridization of said first portion of P2 to said primary TS-DNA thereby forming a TS-DNA-P2 complex;

e) adding one or more second-stage amplification target circles (ATC2) to the mixture in (d) under conditions promoting hybridization of said ATC2 to said second portion of P2 to form a tandem sequence-P2-ATC mixture,

wherein replication of the amplification target circles of (e) results in formation of additional, or, in this case, secondary tandem sequence DNA (page 7, [0057-0062]).

B) The primers are 20-50 bp in length (page 3, [0029]).

C) The primers have segments non-complementary to to a portion of ATC (page 4, [0032]).

D) ATCs are circular, single-stranded DNA molecules between 40 to 1,000 nucleotides (page 4, [0033]).

E) Detection labels can be incorporated into the amplification product using labeled nucleotides (page 4, 5, [0038-0040].

F) The secondary primer (P2) can have separate segments, one which is complementary to the TS-DNA, and the other, at or near the 3'-end, complementary to a portion of ATC, which may be different from the sequence used in the initial step (page 5, 6, [0048]).

G) Either the primers or the ATCs can be placed on a solid support, which can be glass or plastic (page 6, [0051, 0052]).

H) The DNA polymerases useful in the methods include ϕ-29 DNA polymerase, phage M2 DNA polymerase, PRD1 DNA polymerase, VENT DNA polymerase, Klenow fragment of DNA polymerase I, T5 DNA polymerase, T4 DNA polymerase holoenzyme, T7 native polymerase and Bst polymerase (page 6, [0054]).

Claim Rejections - 35 USC § 103 (based on the Lizardi-1 reference)

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 as applied to claim 1 above, and further in view of Sorge et al. (U.S. Patent No. 5,599,921).

A) Claim 8 is drawn to the multiple primers being hexamers, and claim 9 to multiple primers being octamers.

B) Lizardi-1 does not teach hexamers or octamers as primers.

C) Sorge et al. teach families of oligonucleotides from 6 to 8 bp long for use as primers, with sequences substantially complementary to the target DNA (col. 4, lines 27-33; col. 12, lines 8-18).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used primers of Sorge et al. in the amplification method of Lizardi-1. The motivation to do so would have been hexamers and octamers were used to construct of libraries of primers in large quantities for use in amplification reactions.

10. Claims 3, 12-14, 21, 25, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 as applied to claims 1 and 38 above, and further in view of Lizardi-2 (U.S. Patent No. 6,124,120).

A) Lizardi-1 does not teach random primers, linear DNA, duplex DNA with or without nicks, DNA larger than 10,000 nucleotides or DNA with unknown sequence.

B) Lizardi-2 teaches multiple strand displacement amplification (MSDA) method, in which multiple primers are used to amplify DNA strand of interest (col. 2, lines 25-53). The method can be used to amplify any target nucleic acid (col. 5, lines 21-25), including whole genomic DNA using random primers (col. 3, lines 6-10). The DNA molecules to be amplified can be very long, on the order of 50,000 nucleotides (col. 2, lines 64-67).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have included random primers and DNA molecules of Lizardi-2 in the methods of Lizardi-1. The motivation to do so would have been that random primers allowed for amplification of unknown DNA sequences, and using double-stranded DNA targets broadened the range of amplifiable target DNAs.

11. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claims 1 and 3 above.

A) Claim 4 is drawn to multiple primers comprising a mixture of random and specific primers.

B) Lizardi-1 teaches specific primers, whereas Lizardi-2 teaches random primers for the amplification of genomic DNA.

C) Neither Lizardi-1 nor Lizardi-2 teach a mixture of specific and random primers.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used a mixture of specific primers of Lizardi-1 and random primers of Lizardi-2 in the amplification process of Lizardi-1. The motivation to do so would have been that including random primers with specific primers resulted in a very efficient amplification of a target DNA with partially unknown sequence.

12. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claims 12 and 13 above.

A) Claim 15 is drawn to denaturing two strands of a duplex DNA circle in the amplification process.

B) Neither Lizardi-1 nor Lizardi-2 teach denaturation step of the duplex DNA circle.

It was well known and common knowledge in the art that amplification reaction involving primers and double-stranded DNA required separation of the two strands, usually achieved by denaturation. Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to have addded a denaturation step to the amplification reaction when amplifying double-stranded DNA.

13. Claims 32, 41, 46, 47 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 as applied to claims 1, 38 and 44 above, and further in view of Skerra (Nucleic Acids Research, Vol. 20, pp. 3551-3554 (1992).

A) Claims 32 and 41 are drawn to a polymerase with 3'-> 5' exonuclease activity, claim 46 to a modified nucleotide being a 3'-terminal nucleotide, claim 47 to the modified nucleotide being a phosphorotioate nucleotide and claim 59 to the use of a mixture of primers sensitive to and resistant to exonuclease activity.

B) Lizardi-1 does not teach primers resistant to 3'-> 5' exonuclease activity, the resistance being conferred by a phosphorothioate nucleotide at the 3'-end of the primer or the use of a mixture of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction.

C) Skerra teaches that incorporation of a phosphorothioate nucleotide at the 3'-end of the primer renders it inactive to the 3'-> 5' exonuclease activity of DNA polymerases such as Vent and Pfu. The reference also teaches use of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction (page 3553, Fig. 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used primers of Skerra with phosphorothioate nucleotides at the 3'-end in the amplification method of Lizardi-1. The motivation to do so would have been that the 3'-end phosphorothioate nucleotide rendered the primers resistant to 3'-> 5' exonuclease activity the polymerase used in the reaction, resulting in an improved yield of the amplification product.

14. Claims 30, 34 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 as applied to claims 1, 26 and 43 above, and further in view of Cummins et al. (Biochemistry, vol. 35, p. 8734-8741, 1996).

A) Claim 30 is drawn to the nuclease activity being due to endonuclease, claims 34 and 43 are drawn to the nuclease activity due to contaminating nuclease.

B) Lizardi-1 does not teach nucleotides conferring resistance to endonuclease activity due to contaminating nucleases.

C) Cummins et al. teach oligonucleotides containing nucleotides with phosphorodithioate linkages which are resistant to nucleases in nuclear and cytoplasmic extracts (Abstract; Figure 1; page 8738, paragraphs 2-5; page 8739; Table 3).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used phosphorodithioate-modified nucleotides of Cummins et al. in the methods of Lizardi-1. The motivation to do so, expressly provided by Cummins et al., would have been that these nucleotides conferred resistance to oligonucleotides present in nuclear and cytoplasmic extracts and in human serum.

15. Claims 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 as applied to claim 1 above and further in view of Sorge et al. (U.S. Patent No. 5,556,722).

A) Claim 55 is drawn to DNA polymerase without the 3'->5' exonuclease activity, and claim 56 to specific DNA polymerases not exhibiting this activity (e.g. Taq, Tfl, etc.)

B) Lizardi-1 does not teach DNA polymerases without the 3'->5' exonuclease activity (exo(-)).

C) Sorge et al. teaches Taq DNA polymerase which lacks 3'->5' exonuclease activity (col. 5, lines 30-67; col. 6, lines 1-2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used exo(-) Taq DNA polymerase in the method of Lizardi-1. The motivation to do so, expressly provided by Sorge et al., would have been that Taq polymerase was highly processive.

16. Claims 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claim 1 above.

A) Claim 57 is drawn to the DNA polymerase being a reverse transcriptase and claim 58 to the ATC being RNA and the DNA polymerase being a reverse transcriptase.

B) Lizardi-1 does not teach RNA targets or reverse transcriptase.

C) Lizardi-2 teaches that a target DNA can be any nucleic acid (col. 5, lines 21-25) and amplification of cDNA obtained from mRNA (col. 21, lines 14-20).

D) It was well known and common knowledge in the art at the time of the invention that cDNA was obtained from mRNA using reverse transcriptase.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have included RNA targets of Lizardi-2 in the amplification method of Lizardi-1. The motivation to do so would have been that RNA amplification provided a measure of gene expression in cells.

Claim Rejections - 35 USC § 103 (based on the Kingsmore et al. reference)

17. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kingsmore et al. as applied to claim 1 above, and further in view of Sorge et al. (U.S. Patent No. 5,599,921).

A) Claim 8 is drawn to the multiple primers being hexamers, and claim 9 to multiple primers being octamers.

B) Kingsmore et al. do not teach hexamers or octamers as primers.

C) Sorge et al. teach families of oligonucleotides from 6 to 8 bp long for use as primers, with sequences substantially complementary to the target DNA (col. 4, lines 27-33; col. 12, lines 8-18).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used primers of Sorge et al. in the amplification method of Kingsmore et al. The motivation to do so would have been hexamers and octamers were used to construct of libraries of primers in large quantities for use in amplification reactions.

18. Claims 3, 12-14, 21, 25, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kingsmore et al. as applied to claims 1 and 38 above, and further in view of Lizardi-2 (U.S. Patent No. 6,124,120).

A) Kingsmore et al. do not teach random primers, linear DNA, duplex DNA with or without nicks, DNA larger than 10,000 nucleotides or DNA with unknown sequence.

B) Lizardi-2 teaches multiple strand displacement amplification (MSDA) method, in which multiple primers are used to amplify DNA strand of interest (col. 2, lines 25-53). The method can be used to amplify any target nucleic acid (col. 5, lines 21-25), including whole genomic DNA using random primers (col. 3, lines 6-10). The DNA molecules to be amplified can be very long, on the order of 50,000 nucleotides (col. 2, lines 64-67).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have included random primers and DNA molecules of Lizardi-2 in the methods of Kingsmore et al.. The motivation to do so would have been that random primers allowed for amplification of unknown DNA sequences, and using double-stranded DNA targets broadened the range of amplifiable target DNAs.

19. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kingsmore et al. and Lizardi-2 as applied to claims 1 and 3 above.

A) Claim 4 is drawn to multiple primers comprising a mixture of random and specific primers.

B) Kingsmore et al. teach specific primers, whereas Lizardi-2 teaches random primers for the amplification of genomic DNA.

C) Neither Kingsmore et al. nor Lizardi-2 teach a mixture of specific and random primers.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used a mixture of specific primers of Kingsmore et al. and random primers of Lizardi-2 in the amplification process of Kingsmore et al. The motivation to do so would have been that including random primers with specific primers resulted in a very efficient amplification of a target DNA with partially unknown sequence.

20. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kingsmore et al. and Lizardi-2 as applied to claims 12 and 13 above.

A) Claim 15 is drawn to denaturing two strands of a duplex DNA circle in the amplification process.

B) Neither Kingsmore et al. nor Lizardi-2 teach denaturation step of the duplex DNA circle.

It was well known and common knowledge in the art that amplification reaction involving primers and double-stranded DNA required separation of the two strands, usually achieved by denaturation. Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention would to have added a denaturation step to the amplification reaction when amplifying double-stranded DNA.

21. Claims 28, 29, 31-33, 35, 40-42, 44-47 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kingsmore et al. as applied to claims 1, 26 and 38 above, and further in view of Skerra (Nucleic Acids Research, Vol. 20, pp. 3551-3554 (1992).

A) Claim 41 is directed to primers resistant to 3'-> 5' exonuclease activity, claim 46 to a modified nucleotide being a 3'-terminal nucleotide, claim 47 to the modified nucleotide

being a phosphorotioate nucleotide and claim 59 to the use of a mixture of primers sensitive to and resistant to exonuclease activity.

B) Kingsmore et al. do not teach primers resistant to 3'-> 5' exonuclease activity, the resistance being conferred by a phosphorothioate nucleotide at the 3'-end of the primer or the use of a mixture of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction.

C) Skerra teaches that incorporation of a phosphorothioate nucleotide at the 3'-end of the primer renders it inactive to the 3'-> 5' exonuclease activity of DNA polymerases such as Vent and Pfu. The reference also teaches use of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction (page 3553, Fig. 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used primers of Skerra modified with phosphorothioate nucleotides at the 3'-end in the amplification method of Kingsmore et al.. The motivation to do so would have been that the 3'-end phosphorothioate nucleotide rendered the primers resistant to 3'-> 5' exonuclease activity of the polymerase used in the reaction, resulting in an improved yield of the amplification product.

22. Claims 30, 34 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kingsmore et al. as applied to claims 1, 26 and 43 above, and further in view of Cummins et al. (Biochemistry, vol. 35, p. 8734-8741, 1996).

A) Claim 30 is drawn to the nuclease activity being due to endonuclease, claims 34 and 43 are drawn to the nuclease activity due to contaminating nuclease.

B) Kingsmore et al. do not teach nucleotides conferring resistance to endonuclease activity due to contaminating nucleases.

C) Cummins et al. teach oligonucleotides containing nucleotides with phosphorodithioate linkages which are resistant to nucleases in nuclear and cytoplasmic extracts (Abstract; Figure 1; page 8738, paragraphs 2-5; page 8739; Table 3).

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A) Claim 55 is drawn to DNA polymerase without the 3'->5' exonuclease activity, and claim 56 to specific DNA polymerases not exhibiting this activity (e.g. Taq, Tfl, etc.)

B) Kingsmore et al. does not teach DNA polymerases without the 3'->5' exonuclease activity (exo(-)).

C) Sorge et al. teaches Taq DNA polymerase which lacks 3'->5' exonuclease activity (col. 5, lines 30-67; col. 6, lines 1-2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used exo(-) Taq DNA polymerase in the method of Lizardi-1. The motivation to do so, expressly provided by Sorge et al., would have been that Taq polymerase was highly processive.

24. Claims 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kingsmore et al. as applied to claim 1 above, and further in view of Lizardi-2.

A) Claim 57 is drawn to the DNA polymerase being a reverse transcriptase and claim 58 to the ATC being RNA and the DNA polymerase being a reverse transcriptase.

B) Kingsmore et al. do not teach RNA targets or reverse transcriptase.

C) Lizardi-2 teaches that a target DNA can be any nucleic acid (col. 5, lines 21-25) and amplification of cDNA obtained from mRNA (col. 21, lines 14-20).

D) It was well known and common knowledge in the art at the time of the invention that cDNA was obtained from mRNA using reverse transcriptase.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have included RNA targets of Lizardi-2 in the amplification method of Kingsmore et al. The motivation to do so would have been that RNA amplification provided a measure of gene expression in cells.

Double Patenting

25. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

26. Claims 1-15, 20-64 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-67 of U.S. Patent No. 6,323,009 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '009 patent are a species of the claims of the current

application, the only difference being a limitation of the ATC being derived directly from a culture and preferentially amplified over genomic DNA present in the culture.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
December 10, 2001

TS

Kenneth R. Horlick Ph.D.
KENNETH R. HORLICK
PRIMARY EXAMINER
GROUP 1800

12/11/01